DETAILED ACTION

1. Applicant's election with traverse of Claims 1-6 and 9 and SEQ ID No. 2,3,7,8,10,22,25,29, and 34 in the reply filed on 12/08/2007 is acknowledged. The traversal is on the ground(s) that it is not a serious burden to search the sequences because if any single sequence or subcombination of sequences of the elected combination of sequences is not found in the prior art that that search of all combinations that comprise that single sequence would not be found (p. 1 2nd full paragraph and p. 3 1st sentence). This is not found persuasive because as the claims are written they are drawn to any number of possible combinations of single Seq id numbers and combinations of Seq id numbers. Therefore each group of SEQ ID Numbers is distinct and the search for one group would not necessarily provide descriptive information on the other groups. For example a search of the elected combination of SEQ ID No. 2,3,7,8,10,22,25,29, and 34 would not necessarily provide descriptive information on the combination of 11 and 17.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-9 are pending. Claims 7-8 have been withdrawn as being drawn to an nonelected invention. Specifically, the claims are drawn to combinations not elected.

3. An action on the merits for Claims 1-6 and 9 and SEQ ID No. 2,3,7,8,10,22,25,29, and 34 is set forth below.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Specifically p. 25 line 18 contains an hyperlink. Applicant should go through the specification and remove any hyperlinks which are in the instant specification.

Claim Objections

5. Claims 1-6 and 9 are objected to because they specifically recite nonelected subject matter. As stated in the response to the restriction filed 12/08/2007, applicant has elected the specific combination of SEQ ID No. 2,3,7,8,10,22,25,29, and 34. Applicant should amend the claims so that the claims are directed to the elected invention of the specific combination of SEQ ID Nos. Prior to allowance of these claims, the non-elected subject matter will be required to be deleted form the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 9 are rejected over the "it being understood…" phrase in steps b and c. This phrase is limited to when the target genes have a nucleic acid sequence of SEQ ID No. 11, 17, or 37. The claims however were restricted and in the response to the restriction filed 12/08/2007, applicant has elected the specific combination of SEQ ID No. 2,3,7,8,10,22,25,29, and 34. Therefore it is unclear the metes and bounds of this step because the claim only requires SEQ ID No. 2,3,7,8,10,22,25,29, and 34. As such the limitation of "it being understood…" has not been given any patentable weight.

Claims 1-6 and 9 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the process steps of the claims. The preamble states a method for neuroblastoma prognosis, however, the last step is detection of the expression of at least one of said target genes. Therefore there are no active process steps for determining neuroblastoma prognosis.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

Claim 1 is drawn to a method for neuroblastoma prognosis in patient suffering from neuroblastoma comprising extracting any biological material from a biological sample, contacting the sample with specific reagents chosen from reagents specific for the target genes exhibiting SEQ ID No. 2,3, 7,8, 10, 22, 25, 29, and 34, and determining the expression. The breadth of the claim is very large and includes any method which detects SEQ ID No. 2, 3, 7, 8, 10, 22, 25, 29, and 34. Claims 2-3 define the biological sample as any sample taken from any patient. Claims 4-6 defines the reagent. Claim 9 defines the number of reagents to be at least 9.

The claims are broadly drawn correlating any expression level of SEQ ID No.

2,3,7,8,10,22,25,29, and 34 to any prognosis of neuroblastoma by taking any biological material from any biological sample.

When the claims are read in light of the specification, the specification does not provide predictable guidance for correlating any expression level of SEQ ID No. 2,3,7,8,10,22,25,29, and 34 to any prognosis of neuroblastoma.

The art, as presented below, that such correlations are unpredictable and population specific.

Nature of the Invention

The claims are broadly drawn to correlating any expression level of SEQ ID No. 2,3,7,8,10,22,25,29, and 34 to any prognosis of neuroblastoma.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification discloses that there are 6 stages of neuroblastma (stage 1, 2a, 2b, 3, 4, and 4S (p. 2 lines 10-25). The specification asserts that prognosis of neuroblastoma can be determined by analyzing the expression of target genes selected from 37 genes in Table 1 which are expressed differentially depending on whether the patient has good or poor prognosis (p. 3 lines 20-26). However, as discussed in the working example below, the genes were only analyzed with regard to stage 1, 2, 4, and 4S and not Stage 3. Based on the discussions in the art of Takita et al., presented

below, it is unpredictable to correlated prognosis of any tumor sample because it is unpredictable the expression levels in stage 3 tumors. It is not clear if Stage 3 tumors have the same correlative expression as Stage 4 tumors.

The claims are drawn to detection of any prognosis. Any prognosis would encompass a determination of specific stages of tumor. However, the specification only shows guidance to determining good and poor prognosis and not specific prognosis to a particular tumor stage.

Working Examples

23 neuroblastoma samples were collected from patients who were 10.5 months old (p. 23 lines 10-15). 12 samples were in stage 1 or 2, 4 in stage 4s and 7 in stage 4 (p. 23 lines 15-18). Therefore no stage 3 tumors were evaluated.

The specification asserts that patients who died during the study and patients with a stage 4 neuroblastoma were described as patients with poor prognosis (p. 23 lines 23-25). The specification asserts that patients alive and having developed a stage 1,2, and 4s neuroblastma were describes as patients with good prognosis (p. 23 lines 23-25). The specification asserts that the analysis was carried out on 8 poor prognosis patients and 15 good prognosis patients (p. 23 lines 27-28).

Ohira et al. (Cancer Letters 2005 Vol. 228 p. 5) teaches that poor prognosis of neuroblastoma depends on age at diagnosis and advanced tumor stage (3 or 4) (p. 5 2nd column 1st full sentence). However, no stage 3 tumors were used in the instant study so therefore it is unclear if any advanced tumor would have the same expression

levels for each sequence.

The specification discloses that total RNA was extracted (p. 23 line 30) and cDNA was synthesized (p. 24). The specification discloses that expression of approximately 10000 genes was analyzed between good prognosis and poor prognosis patients using the Affymetrix U95Av2 GeneChip (p. 25 lines 5-30).

The specification asserts that relevant genes which were correlated with a poor neuroblastoma prognosis were selected (p. 26 lines 28-30). The specification discloses a list of 37 genes which were differentially expressed in poor prognosis versus good prognosis samples (Table 2 p. 27-28).

The specification discloses the simultaneous expression of the 37 genes of Table 2 in Figure 1 (p. 32 lines 10-25). The specification discloses the simultaneous expression of the 19 genes of Table 4 in Figure 2 (p. 34). The specification discloses the simultaneous expression of the 16 genes of Table 5 in Figure 3 (p. 35). The specification discloses the simultaneous expression of the 12 genes of Table 6 in Figure 4 (p. 36). The specification discloses the simultaneous expression of the 9 genes of Table 7 in Figure 5 (p. 36). Therefore the specification seems to be asserting a correlation of the detection of over or underexpression of 9 genes to prognosis of neuroblastoma in a patient, however, the claims as broadly written encompass at least one gene for the 9 genes listed in Table 7. It is unpredictable that any one of the genes would have the same predictable correlation to prognosis because it is the combination of genes which is correlative and not a single gene.

The specification asserts that detection of only N-myc oncogene gene is not

sufficient for neuroblastoma prognosis (p. 32 lines 25-27). As such the specification indicates that genes which are predictive in a combination would not necessarily provide the same correlation in a single gene study. Therefore the skilled artisan would have to perform undue experimentation to determine which genes in the combination are correlative to prognosis. This would require many intervening steps without a expectation of success.

The predictability or unpredictability of the art and degree of experimentation

Though there is an example in the instant specification, this example has not provided a predictable method to determine prognosis of neuroblastoma based on the unpredictability in the art.

The art teaches associations between expression studies and cancer prognosis are unpredictable and must be reproduced to determine if there is a correlation. Ohira et al. (Cancer Cell April 2005 Vol. 7 p. 337) teaches a method of predicting prognosis of neuroblastoma using cDNA microarrays (abstract). Ohira et al. teaches that gene expression analyses for cancer prognosis prediction should pay close attention to the reproducibility of obtained results (p. 345 1st column last paragraph). Ohira et al. teaches a complete cross validation analysis without introducing any information leakage and an independent test using new samples are necessary (p. 345 last paragraph). Therefore Ohira et al. teaches that reproducibility of expression studies are unpredictable.

Schramm et al. (Clinical Cancer Research 2007 VOl. 13 p. 1459) teaches

generating expression profiles of 47 neuroblastoma patients using Affymetrix U95A chip (abstract). Schramm et al. teaches a table of gene whose correlation was expressed and correlated to neuroblastoma outcome (table 2). Though Schramm et al. teaches the determination of prognosis in the same disease using the same microarray chip, the group of genes Schramm et al. asserts is predictive of prognosis does not overlap the genes asserted by the instant specification. Table 1 of the instant specification lists 37 target genes including SEQ ID No. 2,3, 7,8,10,22,25, 29 and 34 (p. 4 Table 1). The specification asserts that SEQ ID No. 2,3, 7,8, 25, and 34 are from genes whose function is known but which have never been related to neuroblastma (p. 5 lines 1-5). The specification asserts that SEQ ID No. 10,29 are genes whose function is unknown (p. 5 lines 1-5). Therefore, even in the post filing art, the associations of the specific genes expression in the instant specification and prognosis of neuroblastma is not observed in a method with similar steps using the same array. Therefore it is unpredictable that the gene expression associations observed in the instant specification are reproducible in any neuroblastoma tumor sample based upon the unpredictability in the art and post-filing art which does not observe the same gene associations.

Takita et al. (Genes, Chromosomes and Cancer 2004 Vol. 40 p. 120) teaches detection of early and late stage tumors using DNA microarray analysis. Takita et al. teaches that although 9 or the 13 early stage tumors and 4 of the 6 advanced stage tumors were classified as being in the same cluster the remaining tumors showed different expression profiles (abstract). Takita et al. teaches that both early and

advanced stage tumors are heterogeneous in expression (abstract). Therefore Takita et al. teaches that tumor tissue in the same stage can have different expression profiles because of the heterogeneous nature of each tumor stage.

The state of the art teaches that there is a natural variation in gene expression among different individuals and the difficulty in applying gene expression results. The art of Cheung et al (Nature Genetics 2003 Vol. 33 p. 422) teaches that there is natural variation in gene expression among different individuals. Cheung et al teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology 2001 Vol. 195 p. 53). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as

normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology 2001 Vol. 8 p. 37) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). Therefore it is unpredictable with regard to a method of diagnosing depression which gene expression data would be considered a positive correlation with depression. Further, the specification provides no results indicating the fold difference between subjects, which would be considered an association of a gene with depression. The skilled artisan would have to perform undue experimentation to determine which expression levels in each gene would be positively correlated to depression and which changes in expression levels are due to individual differences in the subjects.

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance to correlate any prognosis by detection of expression of any of SEQ ID No. 2,3,7,8,10,22,25,29, or 34.

The art teaches that associations between gene expression and neuroblastoma is unpredictable and is not predictably reproducible.

The skilled artisan, therefore, would have to perform undue experimentation to determine any prognosis of neuroblastma by detection of any level of expression of any of SEQ ID No. 2,3,7,8,10,22,25,29, or 34.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written.

The skilled artisan would have to determine the correlation of expression to any stage of prognosis. The skilled artisan would have to reproducibly correlate expression of any of SEQ ID No. 2,3 , 7, 8, 10, 22, 25, 29, or 34 to any stage of prognosis.

The art teaches that there is a high degree of unpredictability in associations between expression and prognosis. Post-filing art teaches a different set of genes are correlative to prognosis even though Schramm et al used the same Affymetrix chip it his method.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of

guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide a predictable association of any of SEQ ID No. 2, 3, 7, 8, 10, 22, 25, 29, or 34 and determination of any prognosis of neuroblastoma. Further, the art teaches that such correlations are unpredictable and population specific.

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. As discussed in the 35 USC 112/Enablement rejection, the pending claims are rejected as being not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. However, the claims are so broad that they encompass

subject matter which is found in the art, but was not contemplated in the instant specification.

9. Claims 1-6 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (Cancer Research April 2003 Vol. 63 p. 1631).

With regard to Claims 1 and 9, Wang et al. teaches extracting a biological material from a neuroblastoma patient (p. 1631 2nd column Samples and RNA). Wang et al. teaches hybridizing the extracted RNA to the Affymetrix HG_U95Av2 oligonucleotide array (p. 1632 1st column last paragraph). As evidence by the instant specification, the U95Av2 GeneChip comprises probes representing 10000 genes including the genes listed in Table 2 (p. 25 lines 10-15 and Table 2). The genes listed in Table 2 include SEQ ID Nos. 2,3,7,8,10,22,25,29, and 34 and therefore the teaching in Wang et al. of the U95Av2 GeneChip teaches the limitation of contacting the sample with probes specific for SEQ ID Nos. 2,3,7,8,10,22,25,29, and 34. Wang et al. teaches determining the expression profiles (p. 1632 2nd column 1st full paragraph).

With regard to Claim 2, Wang et al. teaches collecting tissue samples (p. 1631 2nd column Samples and RNA).

With regard to Claim 3, Wang et al. teaches that the biological material was RNA (nucleic acids) (p. 1631 2nd column Samples and RNA).

With regard to Claim 4, Wang et al. teaches that specific reagents were probes (p. 1632 1st column last paragraph).

With regard to Claims 5-6, Wang et al. teaches the probes were on an array (e.g. a biochip) (p. 1632 1st column last paragraph).

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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